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Pharmacokinetic evaluation of linezolid administered intravenously in obese patients with pneumonia

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Title page

Title:

Pharmacokinetic evaluation of linezolid administered intravenously in obese patients with pneumonia

Running title:

PKPD of linezolid in obese patients with pneumonia

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Abstract

Objectives: Altered linezolid pharmacokinetics in obese individuals has been hypothesized in previous studies. However, specific dosing recommendations for this population are still lacking. The main goal of this study was to evaluate pharmacokinetic/pharmacodynamic (PKPD) target attainment of a 600 mg intravenous q12h linezolid dose against MRSA in obese patients with pneumonia.

Methods: Fifteen obese pneumonia patients with a confirmed or suspected MRSA involvement treated with 600 mg of intravenous linezolid q12h were studied for three days. Population pharmacokinetic modelling was used to characterize the pharmacokinetic variability and to screen for influential patient characteristics. Monte Carlo simulations were carried out to investigate the PTA and time to target attainment for linezolid dosing against MRSA in the obese population.

Results: A two-compartmental model with linear elimination adequately described the data. Body weight and age both have a significant effect on linezolid clearance. Simulations demonstrate that the probability of attaining PKPD targets is low. Moreover, probability of target attainment (PTA) decreases with weight, and increases with age. Standard linezolid dosing in obese pneumonia patients with MRSA (MICs of 1–4 mg/L) leads to unacceptably low (near zero to 60%) PTA for patients less than 65 years old.

Conclusions: Standard linezolid dosing is likely to provide insufficient target attainment against MRSA in obese patients. Body weight and especially age are important characteristics to be taken into account when dosing linezolid for MRSA infections.

Introduction

The increasing worldwide prevalence of obesity is one of the major burdens on healthcare.^{1, 2} Obese individuals not only have a higher morbidity compared to their non-obese counterparts,^{3, 4} successful treatment may also be hampered by uncertainty in terms of correct drug dosing. Drug dosing in obese patients is generally considered off-label as in most cases obese patients are not included in clinical trials during drug development. As such, the dosing regimens in the label might not be suitable for treating obese patients. Pathophysiology changes in obese patients can have a significant influence on drug distribution and elimination, thereby altering a drug's pharmacokinetics characteristics.⁴⁻⁶ Consequently, overdosing or underdosing is likely to occur in this specific population.³ This issue may especially be of significant clinical relevance for drug treatments in which the effect of the drug is difficult to monitor, for example for antibiotic treatments.

MRSA is a Gram-positive micro-organism that is resistant to most antibiotics.^{7, 8} The increasing prevalence of MRSA is becoming a major therapeutic challenge in hospitals worldwide.^{9, 10} Linezolid, the first antibacterial agent of the group of the oxazolidinones antibiotics, is used to treat pneumonia, skin and soft tissue infections caused by Gram-positive bacteria including MRSA.^{11, 12} As a moderately lipophilic drug (logP of 0.9), linezolid is mainly metabolized in the liver and only 30% of the drug is renally eliminated.¹³ Linezolid has a relatively low (31%) plasma protein binding, and its steady-state volume of distribution is 40 – 50 L, which approximates total body water.¹⁴ For the case of linezolid treatment, the pharmacokinetic/pharmacodynamic (PK/PD) indices strongly correlated with clinical eradication of the invading pathogen, are the time the linezolid concentration remains above the MIC (T>MIC) and the ratio of AUC/MIC over 24 h.^{9, 14}

The current recommended dose of linezolid is 600 mg q12 h *via* intravenous (i.v.) or oral administration. At the moment, there are no specific dosing recommendations for obese patients. Nevertheless, alterations of linezolid pharmacokinetics have been described in obese patients.^{10, 15-20} In two case reports and a small cohort study (n=7), linezolid serum concentrations in obese patients were found to be lower than in normal-weight patients.^{10, 15, 17} Furthermore, Bhalodi *et al.*¹⁸ showed a positive association between the volume of distribution and body weight for moderately and morbidly (otherwise healthy) obese adults. This finding was confirmed in population pharmacokinetic studies of linezolid in normal-weight and obese patients.^{16, 20} However, no information is available on the pharmacokinetics of linezolid in obese patients and the efficacy of a 600 mg q12h dosing for the treatment against MRSA in this specific population.

Therefore, the goal of this study was to determine PKPD target attainment as a surrogate measure for linezolid efficacy in obese pneumonia patients with MRSA involvement. With this study we

aimed: i) to describe the pharmacokinetic variability of linezolid concentrations in a cohort of obese patients using population pharmacokinetic modelling, ii) to evaluate the influence of patient characteristics on the probability of target attainment against MRSA and iii) to evaluate the time course of target attainment within patients throughout therapy.

Patients and methods

Ethics

The research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The study protocol was reviewed and approved by the local institutional review boards of the participating centers (ClinicalTrials.gov Identifier: NCT01805284). Written informed consent was obtained for all patients prior to their enrollment in the study.

Study design and patients

This multi-center and open-label study of linezolid pharmacokinetics was conducted at University Hospital of Larissa, University Hospital of Ioannina, and University Hospital Heraklion, Greece from 2014 to 2016. Patients were enrolled if they met all of the following inclusion criteria: (i) age 18 years or more; (ii) obese ($\text{BMI} > 35 \text{ kg/m}^2$); (iii) confirmed or clinically suspected hospital-, healthcare-, or community-acquired pneumonia; (iv) a confirmed infection for MRSA involvement; (v) admitted to ICU; (vi) decision to start treatment with linezolid therapy. Exclusion criteria were: (i) absence of an arterial line for blood sampling, (ii) anuria, (iii) pregnancy, (iv) need for renal replacement therapy and (v) prior administration of more than one dose of intravenous linezolid.

Drug administration and sample collection

During the study participants received six 600 mg doses of i.v. linezolid q12 h. All doses were administered *via* a 30 min infusion. Blood samples were collected before every drug administration, and at 0.5 (end of the infusion), 0.75, 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12 h after the start of the sixth dose. Blood samples were centrifuged within 30 minutes (4°C , 10 min, $1500\times g$) and transferred into a polystyrene labeled tube and frozen at -20°C until shipment. Samples were pooled and transported on dry ice from the study centers to the Laboratory of Medical Biochemistry and Clinical Analysis, Ghent University where samples were then stored at -80°C until analysis.

Protein binding and sample measurement

Protein binding was determined for each patient using four plasma samples taken from three different days. Briefly, plasma samples were first incubated in a portable mini CO_2 incubator (N-BIOTECK, Korea) for 30 min (37°C , 10% CO_2). After the incubation, 400 μL of plasma was transferred into an Amicon® Ultra-0.5 filter (0.5 mL, 30 KDa; Merck Millipore, Darmstadt, Germany) and centrifuged at $3200 g$ for 10 min at 37°C to obtain the ultrafiltrate (C_{unbound}). A separate plasma

sample was incubated as a quality control to determine the total drug concentration (C_{total}). Protein binding (%) was calculated as $100 \times (1 - C_{unbound}/C_{total})$. The mean value of protein binding was reported for each patient.

Total and unbound linezolid concentrations were measured using a previously developed liquid chromatography-tandem mass spectrometry validated for the simultaneous quantification of β -lactam antibiotics and oxazolidinone antibiotic linezolid in human plasma.²¹ The method bias and precisions for linezolid were less than 9.7% and 11.2%, respectively. The lower limit of quantification of linezolid in plasma was 0.05 mg/L.

Population pharmacokinetic modelling

Software. Nonlinear mixed-effects modelling was performed in NONMEM® (version 7.3, Icon Development Solutions, Ellicott City, MD, USA) employing first-order conditional estimation (FOCE) with interaction, assisted by Perl-Speaks-NONMEM (version 4.60, Uppsala University, Uppsala, Sweden) through the Pirana workbench (version 2.9.6, Pirana Software). Data processing, simulations and plotting were carried out in R® 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Model development. The population model was developed in a stepwise manner with a log-transform-both-sides (LTBS) approach used. Different structural models such as one- and two-compartmental models with linear and/or non-linear eliminations were tested. Inter-individual variability (IIV) and inter-occasion variability (IOV) were assumed to follow a log-normal distribution. The additive error model in the log domain was used throughout the entire process. All PK parameters were allometrically scaled to a total body weight of 70 kg. This means that the allometric exponent was fixed at 1.0 for all volume terms and 0.75 for all clearance terms. Covariates were screened by applying the stepwise forward addition ($p < 0.05$) and backward elimination ($p < 0.01$) procedure. Covariates tested were: age, sex, severity of sepsis episode (sepsis, severe sepsis, and septic shock), creatinine clearance estimated by the Cockcroft & Gault formula,²² serum albumin, alanine transaminase, aspartate aminotransferase, and total bilirubin.

Model selection and evaluation. Model comparison was guided by changes in the objective function value (OFV) between nested models (with a decrease > 3.84 points being statistically significant for the inclusion of a single parameter), the Akaike information criterion (AIC) between non-nested models, the condition number (CN), the relative standard error (RSE) of the parameter estimates, and goodness-of-fit plots.^{23, 24} The final PK model was evaluated using: (i) the visual predictive check (VPC) method (1000 simulations),²⁵ (ii) the normalized prediction distribution errors (NPDE),²⁶ and

(iii) the sampling importance resampling (SIR) procedure for the assessment of parameter uncertainty.²⁷

Prediction of PK/PD target attainment

The PK/PD index of AUC/MIC > 100 and T>MIC of 100% were used for the evaluation of linezolid treatment efficacy in study patients.²⁸ In order to evaluate the observed target attainment, the AUC/MIC and T>MIC values were derived from the post hoc PK parameter estimates for each patient at time intervals between 0 – 24 h, 24 – 48 h, and 48 – 72 h. The MIC of 4 mg/L was chosen because this concentration is considered as the linezolid-susceptible breakpoint for most *S. aureus* isolates including MRSA (from EUCAST website).²⁹ The probability of target attainment was stratified according to patient characteristics to evaluate potential associations.

Monte Carlo simulation

The final population PK model was used to conduct Monte Carlo simulations with the dosage regimen of 600 mg i.v. linezolid q12 h for 3 days. The simulation was performed from 0 to 72 h at two scenarios: (i) 10000 virtual subjects with a fixed age of 60 years (median observed age in this cohort), and weight levels sampled randomly from a uniform distribution ranging from 50 to 160 kg; (ii) 10000 virtual subjects with a fixed weight of 125 kg (median observed weight), and age values sampled randomly from a uniform distribution ranging from 30 to 85 years. The probability of target attainment (PTA) against the MIC values (1, 2, and 4 mg/L) within linezolid susceptible breakpoint for MRSA was calculated at the periods of 0 – 24 h, 24 – 48 h, and 48 – 72 h. According to the MIC distribution of MRSA for linezolid from EUCAST MIC database (<https://mic.eucast.org/Eucast2/regShow.jsp?id=13366>, last accessed August 30th, 2018), the MICs of 1, 2, and 4 mg/L represent 1.40%, 54.08%, 44.46%, and in total 99.88% of the distribution. The cumulative fraction of response (CFR) that accounted for the selected MIC distribution was computed to further qualify linezolid target attainment in patient populations. In all scenarios, the following PKPD targets were used: 100 % T>MIC, AUC/MIC>100 and a combination of AUC/MIC>100 and 100 % T>MIC.

Results

Patient characteristics

A total of 9 males and 6 females were included in the study. All patients completed the study. Recruitment of MRSA-positive, obese patients with pneumonia proved to be problematic. Moreover, linezolid is frequently used empirically in patients with an overt risk profile for MRSA involvement. Therefore, we decided to also include patients who were MRSA-negative. We consider this as a minor protocol violation as we expect no influence on the pharmacokinetic profiling. Consequently,

only two of the included patients were MRSA-positive. A summary of the demographic and clinical characteristics for the included patients are shown in Table 1.

Population pharmacokinetic analysis

A two-compartment model with linear elimination adequately described the linezolid concentrations. An additional IIV term on the residual error variance significantly improved the model fit (drop in OFV of 37.1) and was therefore retained in the model. This term allows for the residual error to vary between individuals. Implementation of IOV on PK parameters was tested and for clearance was found to be statistically significant (drop in OFV of 31.1). Besides the weight effect, we found a linear age effect on clearance (drop in OFV of 9.9). The final linezolid population PK model is summarized with equations 1–4:

$$CL = \theta_{CL} \cdot (1 + \theta_{age} \cdot (Age - 60)) \cdot \left(\frac{Weight}{70}\right)^{0.75} \cdot e^{(\eta_{CL} + \kappa_{CL})} \quad (1)$$

$$V_c = \theta_{V_c} \cdot \left(\frac{Weight}{70}\right) \cdot e^{\eta_{V_c}} \quad (2)$$

$$Q = \theta_Q \cdot \left(\frac{Weight}{70}\right)^{0.75} \quad (3)$$

$$V_p = \theta_{V_p} \cdot \left(\frac{Weight}{70}\right) \quad (4)$$

where CL is linezolid clearance, θ_{age} is age effect parameter on CL, V_c is linezolid central volume of distribution, Q is intercompartmental linezolid clearance, V_p is linezolid peripheral volume of distribution, θ is population estimate, η is IIV, and κ is IOV.

The parameter estimates and associated standard errors for the final model are shown in Table 2. The goodness-of-fit plot shown in Figure 1 suggests an overall good fit of the model to the data. The VPC and the histogram of the NPDEs used as to internally validate the final model are provided as Supplementary data (Figures S1 and S2).

Prediction of PK/PD target attainment

The predicted AUC/MIC and T>MIC values for each patient at day 1, day 2, and day 3, together with the covariates of interest are listed in Table 3. In addition to the PKPD indices which were derived from total concentrations, as recommended in literature,^{11, 28} the unbound fractions of linezolid are reported for future reference. At an MIC of 4 mg/L, the fraction of patients attaining an AUC/MIC>100 increases from 0% on day 1 to 13.3% on days 2 and 3. For the T>MIC of 100%, 26.7%

patients (4/15 patients) reached this target on days 1 and 2. This fraction increased to 33.3% (5/15 patients) on day 3.

Only 13.3% of the patients achieved an AUC/MIC >100 and T $>$ MIC of 100% at steady state. Figure S3 of the supplementary data shows AUC/MIC and T $>$ MIC as a function of the patient characteristics (i.e. weight and age). From this Figure one can see that AUC/MIC values are positively associated with age, and negatively associated with body weight.

Monte Carlo simulation

The indices T $>$ MIC, AUC/MIC, and a combination of them were all used frequently in previous linezolid PKPD studies.^{4,11} It is reported that for linezolid treatment T $>$ MIC and AUC/MIC were highly correlated and performed similarly related to clinical outcomes.²⁸ Herein, we mainly focused on the 100% T $>$ MIC target as linezolid is considered a time-dependent killing antibiotic especially against *S. aureus*.³⁰ The estimated PTAs and CFRs of 100% T $>$ MIC versus weight and age for the three days of treatment against different MIC values are shown in Figure 2. The estimated PTAs and CFRs versus weight and age for the AUC/MIC >100 and combined 100%T $>$ MIC and AUC/MIC >100 targets are supplied in Figures S4 and S5 of the online supplement for reference.

Our PKPD simulations show that patients with large body weight are at a higher risk of not attaining the PKPD targets. The CFR for patients weighting 85 kg (the lowest observed weight) is 27.3% at steady state, and the probability drops to 19.2% for patients weighting 160 kg (the highest observed weight). When target of AUC/MIC >100 is considered, the weight effect on CFR is much more significant with a 3.5-fold drops in probability observed. On the contrary, from the bottom panel in Figure 2 it can be seen that the PKPD target attainment is considerably higher in elderly patients. For patients 30 years old (the lowest observed age), the CFR is extremely low (2.8%), even at steady state. The target attainment rate rises to 98.7% for 85-year old patients (the highest observed age). In all studied scenarios, the PTAs are quite low ($< 60\%$) even at the lowest MIC (1 mg/L) except for the elderly patients (≥ 65 years), regardless of the PKPD indices used.

Discussion

This study aimed to address the question whether a standard 600 mg q12h dosing regimen is efficacious for the treatment of MRSA in obese patients with pneumonia using linezolid PKPD target attainment as a surrogate marker. Our study showed that body weight and age are significantly affecting linezolid pharmacokinetics. Moreover, these patient characteristics have a substantial influence on the probability of attaining PKPD indices associated with therapeutic success.

The pharmacokinetic behavior of linezolid has been studied before in healthy volunteers and obese patients. Abe *et al.*²⁰ and Minichmayr *et al.*³¹ showed, in elderly patients and critically ill patients

respectively, that linezolid clearance decreases with age. On the contrary, in a healthy volunteer study, Sisson *et al.*³² showed no influence of age on clearance. Our results confirm that for obese patients linezolid clearance decreases with age from a value of 15.54 L/h for 30-year old patients to 1.35 L/h in 85 year-old patients. By incorporating a size correction into our model based on allometric theory,³³ we ascertained that our model aligns with earlier work where it was shown that linezolid PKs are influenced by a patient's body weight.^{16, 19, 20, 31} Although creatinine clearance was previously shown to influence linezolid clearance,^{19, 31} it was not retained as a covariate in our model. This was most likely because the majority of patients in our study had mild to moderate renal failure and renal clearance only accounts for 30 % of total drug elimination.

It was previously shown that PTA against pathogens with an MIC of 4 mg/L is low in normal weight and obese patients. Cojutti *et al.*¹⁹ found a PTA of below 10% in overweight and obese patients following a 600mg q12h dosing regimen of linezolid. At the same time, Minichmayr *et al.*³¹ and Yang *et al.*³⁴ found a PTA of near zero in normal weight healthy volunteers. Our findings in obese patients are in line with these previous findings in both normal weight and obese patients. Through PKPD simulations we showed that, depending on the PKPD index, probability of target attainment of typical obese patients (weighting 125 kg and 60 years old) with an MIC of 4 mg/L is zero on day 1 and between 1.03% and 11.88% on day 3 of treatment.

In contrast to these findings, Cojutti *et al.*¹⁹ reported a high cumulative fraction of response (>80%) against MRSA strains in overweight and obese patients. However, in their analysis Cojutti *et al.* used an MIC distribution (0.12 – 2 mg/L, MIC90 of 1 mg/L) of Staphylococci from a local surveillance program. In line with these findings, Puzniak *et al.*³⁵ found a high weight-independent clinical success rate (86.2%) against complicated skin and skin structure infections and nosocomial pneumonia caused by MRSA. However, similar to the work by Cojutti *et al.*, most patients (+/-90%) in the study by Puzniak *et al.* had an MIC less or equal to 1 mg/L. The MRSA MIC distribution for linezolid from the EUCAST MIC database, as used in this study, is significantly different (range from 1 – 4 mg/L, with the MIC90 being 4 mg/L) leading to substantially lower CFRs. We feel that, based on the high prevalence of MRSA with MICs of 2 and 4 mg/L (in total 98.48% of MIC distribution), the approach by Cojutti *et al.*¹⁹ might falsely over-estimate the CFR against MRSA.

When considering our results, the reader should appreciate that our study has some limitations. First, although plasma PK was frequently sampled, the population PK modelling and covariate screening was based on data from only 15 obese patients. This could have prevented the inclusion of more subtle covariate relationships in our model and might have impacted the accuracy of the estimation of inter-individual variability terms. Second, due to difficulties in including patients with a

documented MRSA infection we were not able to study the influence of MRSA infection on the PKs of linezolid and the ensuing effect on PTA. Third, we simulated target attainment for the first three days of treatment whilst it was previously shown that the average PKPD target attainment (e.g. across the first 7 days of therapy) was correlated to clinical cure²⁸. As such, target attainment reported here might falsely under- or over-estimate the probability for clinical cure. Finally, simulated PTAs for normal-weight subjects relied on extrapolation from our study population *via* allometric scaling. Although our extrapolated PTAs are in good agreement with previous reports in normal-weight subjects, our data did not allow us to formally test allometric scaling and the reported results in normal-weight subjects should be interpreted taking into account this uncertainty.

In conclusion, through population PK modelling and PKPD simulations we demonstrated that a 600mg q12h dosing regimen is unlikely to be efficacious against MRSA infections in obese patients with pneumonia. We feel that our results, in combination with earlier reports on low target attainment against MRSA in normal-weight and obese patients, provide sufficient scrutiny to advice against standard linezolid dosing for the treatment of MRSA in obese patients.

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Other members of the LIMOP study collaborators

Epameinondas Zakynthinos, University Hospital of Larissa, Greece; Dimitrios Georgopoulos, University Hospital of Crete, Greece; Athanasios Papathanasiou, University Hospital of Ioannina, Greece; Kostoula Arvaniti and Dimitrios Matamis, Papageorgiou General Hospital of Thessaloniki, Greece; Anna Spring and Vasileios Bekos, Naval Hospital of Athens, Greece; Apostolos Komnos and Tilemachos Zafeiridis, General Hospital of Larissa, Greece; Dirk Vogelaers, Ghent University Hospital, Belgium.

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Transparency declarations

None to declare.

Author contributions

Feifan Xie analyzed the plasma samples, developed the population pharmacokinetic model and prepared the first draft of the manuscript. Pieter Colin was a principal investigator for the project, supervised Feifan Xie on sample measurement, modelling and preparation of the manuscript,

reviewed and approved final version of the manuscript. Konstantinos Mantzarlis coordinated the project at the Larissa site and approved the final version of the manuscript. Polychronis Malliotakis coordinated the project at the Irakleio site and approved the final version of the manuscript. Vasileios Koulouras coordinated the project at the Ioannina site and approved the final version of the manuscript. Despoina Koulenti and Stijn Blot were Principal Investigators, coordinated the whole project, reviewed the manuscript and approved the final version. Koen Boussery and Jan Van Bocxlaer coordinated the whole project, reviewed the manuscript and approved the final version.

Supplementary data

Figures S1 – S5 are available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

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35. Puzniak LA, Morrow LE, Huang DB et al. Impact of weight on treatment efficacy and safety in complicated skin and skin structure infections and nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus*. *Clin Ther* 2013; **35**: 1557-70.

412 Table 1. Baseline characteristics of study patients (n=15)

Characteristic	n (%) or median (IQR ^a)
Age (years)	64.5 (56.2 – 71.0)
Male/female	9 (60)/6 (40)
MRSA microbiology: positive/negative	2 (13.3) /13 (86.7)
Body weight (kg)	125.0 (112.5 – 133.0)
Height (cm)	169.0 (160.0 – 174.5)
BMI (kg/m ²)	40.0 (37.8 – 49.4)
Obese (BMI>35 kg/m ²) / morbidly obese patients (BMI>40 kg/m ²)	5 (33.3)/10 (66.7)
Sepsis episode: sepsis/severe sepsis/septic shock	5 (33.3)/7 (46.7)/3 (20)
Serum creatinine (mg/dL)	1.42 (1.16 – 1.64)
Creatinine clearance (Cockcroft & Gault, mL/min)	80.8 (66.7 – 107.6)
Serum albumin (g/dL)	3 (2.5 – 3.3)
Alanine transaminase (IU/L)	35 (22.2 – 40.5)
Aspartate aminotransferase (IU/L)	45 (22.5 – 53.5)
Total bilirubin (mg/dL)	0.61 (0.46 – 1.09)
Trough total concentration at 72 h (mg/L)	0.95 (0.33 – 2.75)
Unbound fraction (%)	83.1 (78.9 – 87.3)

^aIQR, interquartile range.

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Table 2. Population parameter estimates of the final pharmacokinetic model and the results of the sampling importance resampling (SIR) approach

Parameter	Final pharmacokinetic model	SIR results	
	Estimate (RSE%) [Shrinkage%]	Median	95% CI
Fixed effects			
θ_{CL} (L/h/70 kg)	7.8 (12.1)	8.1	6.2 – 10.1
θ_{age} (1/year)	-0.0331 (4.6)	-0.0331	-0.0367 – -0.0300
V_c (L/70 kg)	14.3 (5.3)	14.3	12.8 – 15.8
Q (L/h/70 kg)	65.1 (12.8)	67.8	53.2 – 85.1
V_p (L/70 kg)	23.8 (6.5)	24.2	21.3 – 27.0
Inter-individual variability (IIV)			
CL (CV%)	66.9 (36.2) [0.1]	72.8	47.6 – 111.1
V_c (CV%)	43.5 (33.8) [1.1]	46.2	35.9 – 77.3
ω_{CL,V_c}	0.23 (34.4)	0.26	0.12 – 0.47
IIV on residual error magnitude	96.5 (28.3)	98.9	60.8 – 153.6
Inter-occasional variability (IOV)			
CL (CV%)	16.1 (47.5) [3-46]	16.7	11.9 – 22.1
Residual variability			
Proportional error ^a (%)	15.9 (7) [0.6]	15.8	13.6 – 18.0

RSE, relative standard error; CI, confidence intervals; θ_{CL} , typical clearance; θ_{age} , age effect parameter on clearance; V_c , volume of distribution of the central compartment; Q , inter-compartmental clearance between central and peripheral compartment; V_p , volume of distribution of the peripheral compartment; ω_{CL,V_c} , covariance between the variances of CL and V_c .

CV (%) is calculated according to: $CV (\%) = \sqrt{\exp(\omega^2) - 1} \times 100\%$. ω^2 : the variance estimate in the log-domain.

^a An additive error model in the log-transformed domain was used to characterize the residual unexplained variability, which approximates to a proportional error in the normal domain.

450 Table 3. Calculated PKPD indices in study patients together with the selected patient characteristics

Patient ID	AUC _{0-24h} /MIC	AUC _{24-48h} /MIC	AUC _{48-72h} /MIC	T _{0-24h} >MIC (h)	T _{24-48h} >MIC (h)	T _{48-72h} >MIC (h)	Age (years)	Weight (kg)	Unbound fraction (%)
1	11.6	11.9	13.5	3.9	4.0	4.7	48.3	115	79.1
2	23.6	24.2	22.9	9.5	9.8	9.1	58.1	129	69.1
3	16.5	15.8	16.9	5.8	5.5	6.1	54.4	118	89.0
4	70.9	126.5	161.8	24.0	24.0	24.0	84.7	87	86.2
5	31.3	36.2	35.2	15.2	17.3	16.6	45.8	151	83.1
6	23.8	28.7	37.8	10.0	13.5	19.5	60.6	135	87.5
7	6.8	7.9	8.0	1.5	1.8	1.9	64.5	125	70.7
8	32.8	43.5	43.1	15.1	21.9	20.7	72.2	105	85.4
9	17.8	15.7	14.8	6.5	5.6	5.1	59.5	110	93.5
10	48.9	69.3	76.2	24.0	24.0	24.0	75.7	118	80.2
11	48.6	64.2	67.4	24.0	24.0	24.0	67.7	131	71.9
12	13.4	18.1	17.8	3.6	6.3	6.3	69.9	160	78.7
13	33.0	42.5	52.0	16.6	22.5	24.0	72.2	135	91.1
14	9.7	10.4	10.7	2.9	3.2	3.4	32.1	130	82.3
15	71.4	102.1	119.8	24.0	24.0	24.0	68.8	103	87.0

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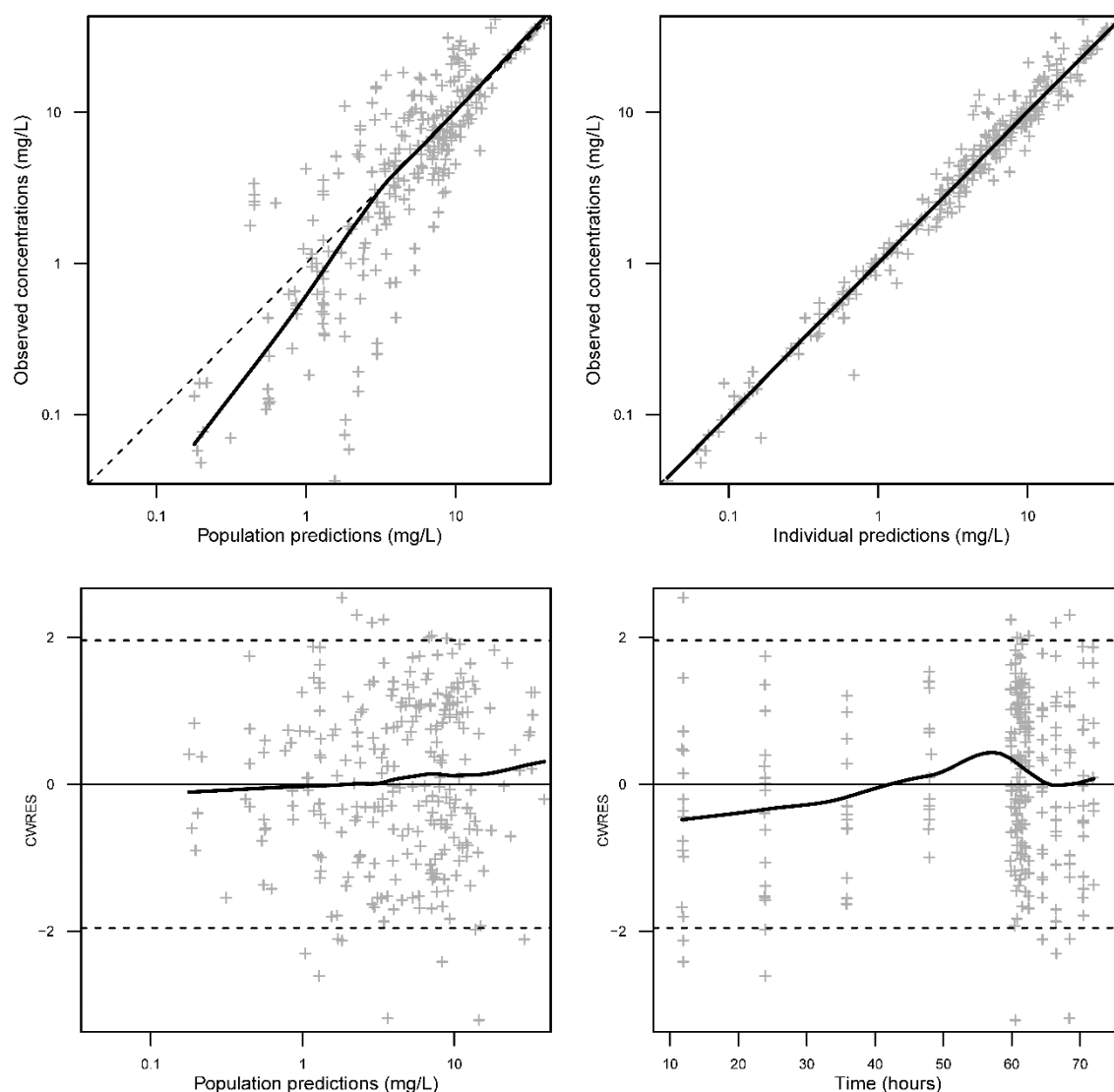
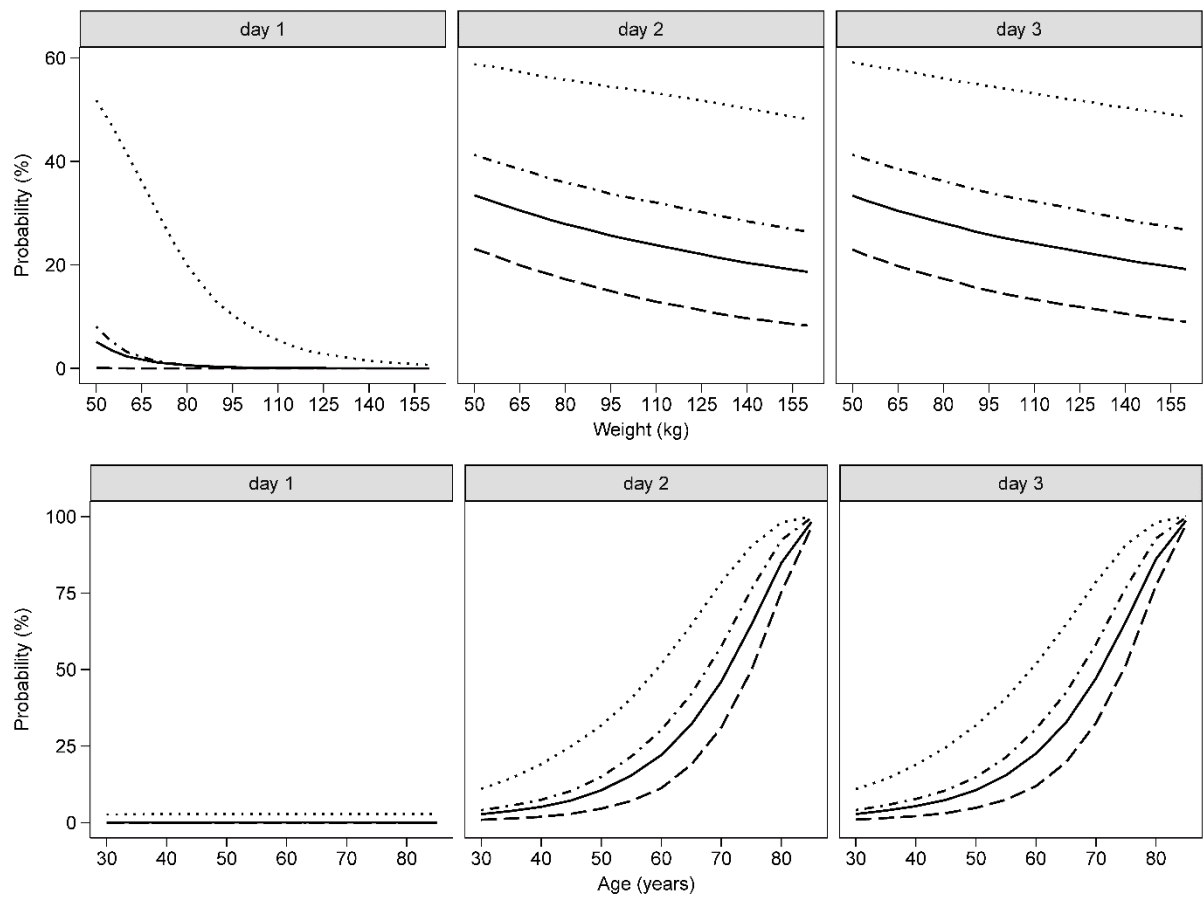


Figure 1. Goodness-of-fit plots of the final linezolid population pharmacokinetics model. Top left panel: Observed concentrations versus population predictions of linezolid in plasma; Top right panel: Observed concentrations versus individual predictions of linezolid in plasma; Bottom left panel: conditional weighted residuals (CWRES) versus population predicted linezolid concentrations; Bottom right panel: CWRES versus time.



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478 Figure 2. The probability of target attainment (PTA) and cumulative fraction of response (CFR) versus
 479 weight (top panels) and age (bottom panels) against different MIC values on three consecutive days
 480 for 600 mg every 12h linezolid treatment. PTA was determined using T>MIC of 100% at MICs of 1
 481 (dotted line), 2 (dotdash line), and 4 (longdash line) mg/L. CFR was shown as the solid line. The
 482 simulated population in the upper rows were at a fixed age of 60 years and in the bottom rows were
 483 at a fixed weight of 125 kg.